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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/822,205	ZHAO ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006 and 12 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *20 and 22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Election/Restrictions

Claims 20 and 22-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. The subject matter of claim 8 directed to SEQ ID NO: 3 is also withdrawn as being a non-elected sequence. Applicant timely traversed the restriction (election) requirement in the reply filed on January 27, 2006.

Specification

The amendment filed September 20, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment attempts to amend the specification at pages 11 and 12 by changing the "X" to "M" in the phosphate group of several structures. Applicants assert this change does not introduce new matter because the use of X in these structures was an informality that would be readily recognized by the ordinary artisan. This is not persuasive because there is no evidence or reasoning presented describing why one would make the

assumption that positions designated as X were meant to be M and were not intended to define a substituent distinct from M.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to arguments: Claim Objections

Claim 3 is objected to because of the following informalities: this claim is ungrammatical because the word "is" in line 1 is unnecessary. Appropriate correction is required. Applicants state in the remarks filed September 20, 2006 that this objection has been overcome by amendment, but no amendment to this claim has been made.

Claim 10 is objected to because it is repetitive. The claim recites four structures. However, three of these, (i), (ii) and (iv), are identical structures comprising in order an oligonucleotide, a linker, a spacer, a polymer residue, a linker, a spacer and an oligonucleotide. While the oligonucleotide portions of the different structures are written as combinations of X_2 and X_3, the structures are identical because the convention in the art is to write oligonucleotides in the 5'-3' orientation, a convention specifically referred to at page 11 of the specification, neither the specification nor the claims defines either X_2 or X_3 as different from this convention. Applicants argue in the remarks filed September 20, 2006 that the structures of this claim are not identical and that the direction of the oligonucleotide codings are specified. However, " 3' " is not a direction and therefore this claim does not clearly distinguish the recited structures.

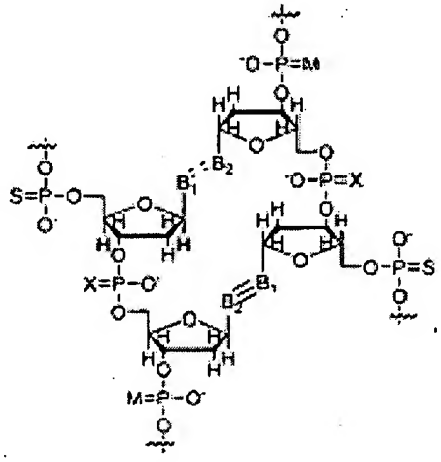
New Claim Objections

Claims 1 and 2 are objected to because of the following informalities: in claim 1, the definition of L_3 as "-$QCR_{50}R_{51})_q$NHC(O)$(CR_{52}R_{53})_r$" that appears in line 14 is missing an open parenthesis following "Q" and claim 2 lacks a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 2, 4 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained for the reasons set forth in the office action mailed July 24, 2006 and reiterated below.

Claim 2 recites several structures that can be the nucleotide recited in claim 1. This claim is indefinite because the structure shown below apparently shows two strands of nucleotides and it is unknown which nucleotides represent those recited in the claim and it is also unknown if the other nucleotides are also modified with linkers and spacers to be prodrugs.



Claim 4 recites the limitation "M". There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites that in SEQ ID NO: 4 n is "any compatible nucleotide". This phrase is indefinite because there is no art recognized meaning for the term "compatible nucleotide" in the context of the claim.

Response to arguments

With regard to the rejection of claim 2, applicants state that the dashed lines noted in the rejection indicate standard interchain bonding of Watson-Crick base pairing, and this is acknowledged but does not define what portion of the structure is part of the polymeric prodrug. The structure shows two strands of nucleotides and it is unknown which nucleotides are those recited in the claim and whether or not the other nucleotides are also modified with linkers and spacers to be prodrugs. Does this structure indicate an oligonucleotide base paired to one nucleotide or is this meant to indicate be a double stranded oligonucleotide, each strand of which is modified to comprise a polymeric prodrug?

With regard to claim 4, applicants argue the limitation of this claim finds antecedent basis in claim 1, however, even as amended the only appearance of this letter in claim 1 is a lowercase "m" that is an integer defining the length of L_3. The limitation of claim 4 defining M as S makes no sense in this context.

With regard to claim 8, applicants have changed the previously cited "X" to n to conform to SEQ ID NO: 4 as it appears in the sequence listing, but this amendment

does not overcome the lack of an art recognized meaning for the term "compatible nucleotide" in the context of this claim.

New Claim Rejections - 35 USC § 112

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 2 has been amended to recite structures wherein positions designated as "X" are changed to "M". Applicants assert this change does not introduce new matter because the use of X in these structures was an informality that would be readily recognized by the ordinary artisan. This is not persuasive because there is no evidence or reasoning presented describing why one would make the assumption that positions designated as X were meant to be M and were not intended to define a substituent distinct from M.

Claim Rejections - 35 USC § 103

Claims 1-3, 5-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teng et al. (US 6,887,906) in view of Greenwald et al. (US 6,303,569) and Dandliker et al. (US 5,707,813).

The claimed invention is directed to prodrug compounds comprising an oligonucleotide and one or more polymers, linking moieties and spacers. In specific

embodiments the oligonucleotide component is a phosphorothioate and may be an antisense, the linking moiety comprises an aromatic group, the antisense sequence is SEQ ID NO: 1 and the polymer component is a polyalkylene oxide such as polyethylene glycol.

Teng et al. teach compositions of antisense oligonucleotides useful for therapeutic purposes. One of these is a sequence 18 bases in length targeted to bcl-2 and designated as SEQ ID NO: 34, which is identical to instant SEQ ID NO: 1. At column 10 Teng et al. teach that the antisense compounds of the invention can comprise modified linkages such as phosphorothioates. At column 17, lines 58-67 Teng et al. teach that the oligonucleotides of their invention can be provided in prodrug form, an inactive form that is converted to active form within a cell. Teng et al. do not explicitly teach the use of polymeric prodrugs.

Greenwald et al. teach that poor solubility and rapid degradation *in vivo* are recognized problems of some therapeutic agents. One solution to these problems is the use of prodrugs; inactive forms of a drug that are metabolized within the body to form the active agent. The use of prodrugs can allow one to increase the solubility and lifetime of a drug. Greenwald et al. teach polymeric prodrugs illustrated at columns 2-3 as formula I. The prodrugs comprise a polymer region, designated as R_{11}, a linker comprising an aromatic group and a drug component designated as B. At columns 18-19 Greenwald et al. teach that the drug component B includes nucleic acids such as DNA or RNA. At columns 9-10 Greenwald et al. teach that polyalkylene oxides such as polyethylene glycol are a preferred polymer component of the prodrug and that these polymers have molecular weights in the range of 2000-100000. The polymer

component can have a capping structure such as an alkyl group or can comprise the structure shown as figure II, which would produce a bis-prodrug, wherein the two drug components are identical or different.

It was well known in the art at the time of invention to employ linkers as a component of an oligonucleotide conjugate. For example Dandliker et al. teach that a commercially available reagent can be used to produce an oligonucleotide having a hexylamine at the 5' terminus. This linker allows the skilled artisan to produce a variety of conjugates by attaching different groups to the oligonucleotide through reaction with the primary amine.

It would have been obvious to one of ordinary skill in the art at the time of invention to produce the bcl-2 sequence of Teng et al. in prodrug form as a polymeric prodrug, including a polymeric bis-prodrug, as taught by Greenwald et al. Teng et al. provide a motivation to make the antisense sequence as a prodrug by explicitly suggesting their oligonucleotides be formulated as prodrugs. Greenwald et al. provide a motivation to make polymeric prodrugs by teaching that polymeric prodrugs allow an increase in the solubility and stability of therapeutic agents and explicitly suggest their use with nucleic acid drugs. It is further obvious to use hexylamine linkers as a component of the prodrug because Dandliker et al. teach that the person of ordinary skill in the art would be familiar with the use of such linkers due to the commercial availability of reagents that make such linkers and the extensive use of hexylamine linkers for producing a variety of oligonucleotide conjugates. One of ordinary skill in the art would have had a reasonable expectation of success in producing a polymeric

prodrug of the bcl-2 sequence because Greenwald et al. provide detailed guidance for the synthesis of polymeric prodrugs.

Thus, the invention of claims 1-3, 5-19 and 21 would have been obvious, as a whole, at the time of invention.

Response to Arguments

Applicants' arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicants traverse the 103 rejection by arguing that nowhere in the references is it taught or suggested to make the invention of claim 1 and asserting none of the cited reference would have taught the compound of claim 1. Applicants appear to be arguing there is no motivation to combine the references. The motivation to combine the references is found in the Teng and Greenwald references, with Teng et al. providing a motivation to make the antisense sequence as a prodrug by explicitly suggesting oligonucleotides be formulated as prodrugs. Greenwald et al. provide a motivation to make polymeric prodrugs by teaching that polymeric prodrugs allow an increase in the solubility and stability of therapeutic agents and explicitly suggesting their use with nucleic acid drugs. Greenwald et al. further teach that polyalkylene oxides such as polyethylene glycol are a preferred polymer component of the prodrug. Based on the teachings of Dandliker et al. that hexylamine linkers were known and used as components of oligonucleotide conjugates, one of ordinary skill in the art would have further been motivated to include these in prodrugs.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
May 15, 2007

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER